## HIGHLIGHTS OF PRESCRIBING INFORMATION

**These highlights do not include all the information needed to use MIRAPEX ER safely and effectively. See full prescribing information for MIRAPEX ER.**

**MIRAPEX® ER™ (pramipexole dihydrochloride) extended-release tablets**

**Initial U.S. Approval: 1997**

### RECENT MAJOR CHANGES

| | |
|---|---|
| Dosage and Administration, Dosing for Parkinson's Disease (2.2) | 2/2010 |
| Warnings and Precautions, Impulse Control/Compulsive Behaviors (5.8) | 2/2010 |

### INDICATIONS AND USAGE

MIRAPEX ER is a non-ergot dopamine agonist indicated for the treatment of the signs and symptoms of early Parkinson's disease (1)

### DOSAGE AND ADMINISTRATION

- MIRAPEX ER tablets are taken once daily, with or without food (2.1)
- Tablets must be swallowed whole and must not be chewed, crushed, or divided (2.1)
- Starting dose is 0.375 mg given once daily (2.2)
- Dose may be increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75 mg increments up to a maximum recommended dose of 4.5 mg per day. Assess therapeutic response and tolerability at a minimal interval of 5 days or longer after each dose increment. (2.2)
- Patients may be switched overnight from immediate-release pramipexole tablets to MIRAPEX ER tablets at the same daily dose. Dose adjustment may be needed in some patients (2.3)
- MIRAPEX ER tablets should be discontinued gradually over a period of one week (2.2)

### DOSAGE FORMS AND STRENGTHS

Extended-release tablets: 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, and 4.5 mg (3)

### CONTRAINDICATIONS

None (4)

### WARNINGS AND PRECAUTIONS

- Falling asleep during activities of daily living: Sudden onset of sleep may occur without warning. Advise patients to report symptoms to the prescriber. (5.1)
- Symptomatic orthostatic hypotension: Monitor closely especially during dose escalation (5.2)
- Hallucinations: May occur. Risk increases with age (5.3)
- Dyskinesia: May be caused or exacerbated by MIRAPEX ER (5.4)
- Renal impairment: No data available in moderate to severe renal impairment (5.5)
- Events reported with dopaminergic therapy: Include withdrawal-emergent hyperpyrexia and confusion, fibrotic complications, melanoma, and impulse control/compulsive behaviors (5.8, 17.4)

### ADVERSE REACTIONS

- Most common adverse events (incidence ≥5% and greater than placebo) in early Parkinson's disease without levodopa were somnolence, nausea, constipation, dizziness, fatigue, hallucinations, dry mouth, muscle spasms, and peripheral edema (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.**

**To report SUSPECTED ADVERSE REACTIONS, contact at or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**

### DRUG INTERACTIONS

- Dopamine antagonists: May diminish the effectiveness of pramipexole (7.1).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**

**Revised: 02/2010**

**FULL PRESCRIBING INFORMATION: CONTENTS ***



*** Sections or subsections omitted from the full prescribing information are not listed**

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## FULL PRESCRIBING INFORMATION

## 1 INDICATIONS AND USAGE

MIRAPEX® ER™ tablets are indicated for the treatment of the signs and symptoms of early idiopathic Parkinson's disease.
MIRAPEX ER is not indicated in advanced Parkinson's disease.

## 2 DOSAGE AND ADMINISTRATION

### 2.1 General Dosing Considerations

MIRAPEX ER tablets are taken orally once daily, with or without food.
MIRAPEX ER tablets must be swallowed whole and must not be chewed, crushed, or divided.
If a significant interruption in therapy with MIRAPEX ER tablets has occurred, re-titration of therapy may be warranted.

### 2.2 Dosing for Parkinson's Disease

The starting dose is 0.375 mg given once per day. Based on efficacy and tolerability, dosages may be increased gradually, not more frequently than every 5 to 7 days, first to 0.75 mg per day and then by 0.75 mg increments up to a maximum recommended dose of 4.5 mg per day.
In clinical trials, dosage was initiated at 0.375 mg/day and gradually titrated based on individual therapeutic response and tolerability. Doses greater than 4.5 mg/day have not been studied in clinical trials. Patients should be assessed for therapeutic response and tolerability at a minimal interval of 5 days or longer after each dose increment [*see Clinical Studies (14)*]. In a clinical trial with healthy volunteers, where dosages were titrated faster than recommended (every 3 days up to 4.5 mg per day) increases in blood pressure and heart rate were observed [*see Clinical Pharmacology (12.2)*].
Due to the flexible dose design used in clinical trials, specific dose-response information could not be determined [*see Clinical Studies (14)*].
When discontinuing therapy with MIRAPEX ER, taper the dose gradually over a period of one week. In some studies with immediate-release pramipexole tablets, however, abrupt discontinuation was uneventful.
*Dosing in Patients with Renal Impairment*
The elimination of pramipexole is dependent on renal function [*see Clinical Pharmacology (12.3)*]. Patients with mild renal impairment (a creatinine clearance above 50 mL/min) require no reduction in daily dose.
In patients with moderate renal impairment (creatinine clearance between 30 and 50 mL/min), MIRAPEX ER tablets should initially be taken every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week, and before any additional titration in 0.375 mg increments up to 2.25 mg per day. Dose adjustment should occur no more frequently than at weekly intervals.

MIRAPEX ER tablets have not been studied in patients with severe renal impairment (creatinine clearance <30 mL/min) or patients on hemodialysis, and are not recommended in these patients.

### 2.3 Switching from Immediate-Release Pramipexole Tablets to MIRAPEX ER

Patients may be switched overnight from immediate-release pramipexole tablets to MIRAPEX ER tablets at the same daily dose. When switching between immediate-release pramipexole tablets and MIRAPEX ER tablets, patients should be monitored to determine if dosage adjustment is necessary [*see Clinical Studies (14)*].

## 3 DOSAGE FORMS AND STRENGTHS

0.375 mg white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.375" on the other side

0.75 mg white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.75" on the other side

1.5 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "1.5" on the other side

3 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "3.0" on the other side

4.5 mg white to off-white, oval, extended-release tablets debossed with "ER" on one side and "4.5" on the other side

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Falling Asleep During Activities of Daily Living

Patients treated with pramipexole have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on pramipexole tablets, some perceived that they had no warning signs such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events had been reported as late as one year after the initiation of treatment. In a placebo-controlled clinical trial in early Parkinson's disease, the sudden onset of sleep or sleep attacks were reported in 7 of 223 (3%) patients treated with MIRAPEX ER tablets compared to 1 of 103 (1%) patients on placebo.

In early Parkinson’s disease, somnolence was reported in 36% of 223 patients treated with MIRAPEX ER, median dose 3.0 mg/day, compared to 15% of 103 patients on placebo. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with MIRAPEX ER tablets, advise patients of the potential to develop drowsiness, and specifically ask about factors that may increase the risk such as the use of concomitant sedating medications or alcohol, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine) [*see Clinical Pharmacology (12.3)*]. If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX ER tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX ER tablets, advise patients not to drive and to avoid other potentially dangerous activities. While dose reduction reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

### 5.2 Symptomatic Orthostatic Hypotension

Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, Parkinson's disease patients being treated with dopaminergic agonists, including MIRAPEX ER, ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk [*see Patient Counseling Information (17.5)*]. In a placebo-controlled clinical trial in early Parkinson’s disease, symptomatic orthostatic hypotension was reported in 7 of 223 (3%) patients treated with MIRAPEX ER tablets compared to 1 of 103 (1%) patients on placebo. No patient on MIRAPEX ER tablets discontinued treatment due to hypotension.

### 5.3 Hallucinations

In a placebo-controlled clinical trial in early Parkinson's disease, hallucinations (visual or auditory or mixed) were reported in 11 of 223 (5%) patients treated with MIRAPEX ER tablets compared to 1 of 103 (1%) patients receiving placebo. Hallucinations led to discontinuation of treatment in 2 of 223 (1%) patients on MIRAPEX ER tablets.

Age appears to increase the risk of hallucinations attributable to pramipexole. In a placebo-controlled clinical trial in early Parkinson's disease, hallucinations were reported in 7 of 92 (8%) patients ≥65 years of age taking MIRAPEX ER tablets compared to 4 of 131 (3%) patients <65 years of age taking MIRAPEX ER tablets.

### 5.4 Dyskinesia

MIRAPEX ER tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia.

### 5.5 Renal Impairment

The elimination of pramipexole is dependent on renal function [*see Clinical Pharmacology (12.3)*]. Patients with mild renal impairment (a creatinine clearance above 50 mL/min) require no reduction in daily dose. MIRAPEX ER tablets have not been studied in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) or on hemodialysis [*see Dosage and Administration (2.2), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)*].

### 5.6 Rhabdomyolysis

In the clinical development program for immediate-release pramipexole tablets, a single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication.

Advise patients to contact a physician if they experience any unexplained muscle pain, tenderness, or weakness, as these may be symptoms of rhabdomyolysis.

### 5.7 Retinal Pathology in Rat

*Animal Data*

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in a 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. The potential significance of this effect for humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved [*see Nonclinical Toxicology (13.2)*].

### 5.8 Events Reported with Dopaminergic Therapy

Although the events enumerated below may not have been reported with the use of pramipexole in its development program, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

*Withdrawal-Emergent Hyperpyrexia and Confusion*

Although not reported with pramipexole in the clinical development program, a symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.

*Fibrotic Complications*

Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis, and cardiac valvulopathy have been reported in patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, non-ergot derived dopamine agonists can cause them is unknown.

Cases of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis have been reported in the postmarketing experience with immediate-release pramipexole tablets. While the evidence is not sufficient to establish a causal relationship between pramipexole and these fibrotic complications, a contribution of pramipexole cannot be completely ruled out.

*Melanoma*
Epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, is unclear.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using MIRAPEX ER tablets for *any* indication. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

*Impulse Control/Compulsive Behaviors*
Cases of pathological gambling, hypersexuality, compulsive eating (including binge eating), and compulsive shopping have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.

## 6 ADVERSE REACTIONS
The following are discussed in greater detail in other sections of the labeling:
- Falling Asleep During Activities of Daily Living [*see Warnings and Precautions (5.1)*]
- Symptomatic Orthostatic Hypotension [*see Warnings and Precautions (5.2)*]
- Hallucinations [*see Warnings and Precautions (5.3)*]
- Dyskinesia [*see Warnings and Precautions (5.4)*]
- Renal Impairment [*see Warnings and Precautions (5.5)*]
- Rhabdomyolysis [*see Warnings and Precautions (5.6)*]
- Retinal Pathology in Rat [*see Warnings and Precautions (5.7)*]
- Events Reported with Dopaminergic Therapy [*see Warnings and Precautions (5.8)*]

### 6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug (or of another development program of a different formulation of the same drug) and may not reflect the rates observed in practice.
During the premarketing development of MIRAPEX ER tablets, patients with early Parkinson's disease were treated with MIRAPEX ER tablets, placebo, or immediate-release pramipexole tablets. In addition, a randomized, double-blind, parallel group trial was conducted in 156 early Parkinson's disease patients (Hoehn & Yahr Stages I-III) to assess overnight switching of immediate-release pramipexole tablets to MIRAPEX ER tablets. In this latter study, concomitant treatment with stable doses of levodopa, monoamine oxidase B inhibitor (MAOB-I) drugs, anticholinergics, or amantadine, individually or in combination, was allowed.
*Early Parkinson's Disease*
The most commonly observed adverse events (≥5% and more frequent than placebo) after 33 weeks of treatment with MIRAPEX ER tablets in the trial of early Parkinson's disease patients were somnolence, nausea, constipation, dizziness, fatigue, hallucinations, dry mouth, muscle spasms, and peripheral edema.
Twenty four of 233 (11%) patients treated with MIRAPEX ER tablets for 33 weeks discontinued treatment due to adverse events compared to 4 of 103 (4%) patients who received placebo and approximately 20 of 213 (9%) patients who received immediate-release pramipexole tablets. The adverse events most commonly causing discontinuation of treatment with MIRAPEX ER tablets was nausea (2%).
Table 1 lists adverse events that occurred with a frequency of at least 2% with MIRAPEX ER (and were more frequent than with placebo) during 33 weeks of treatment in a double-blind, placebo-controlled study in early Parkinson's disease. In this study, patients did not receive concomitant levodopa; however, levodopa was permitted as rescue medication. Adverse events were usually mild (38%) or moderate (41%) in intensity.
Table 1 Treatment-Emergent Adverse-Event Incidence in a Double-Blind, Placebo-Controlled 33 Week Trial in Early Parkinson's Disease (Events ≥2% of Patients Treated with MIRAPEX ER or Immediate Release Pramipexole and >% with Placebo)

| **Body System / Adverse Event** | **Placebo** | **MIRAPEX ER** | **Immediate Release Pramipexole** |
|---|---|---|---|
| | **(n=103)** | **(n=223)** | **(n=213)** |
| | **%** | **%** | **%** |
| **Nervous system disorders** | | | |

| | | | |
|---|---|---|---|
| Somnolence | 15 | 36 | 33 |
| Dizziness | 7 | 12 | 12 |
| Tremor | 1 | 3 | 3 |
| Headache | 6 | 3 | 7 |
| Balance disorder | 1 | 2 | 0 |
| Memory impairment | 1 | 0 | 2 |
| **Gastrointestinal disorders** | | | |
| Nausea | 9 | 22 | 24 |
| Constipation | 2 | 14 | 12 |
| Dry mouth | 1 | 5 | 4 |
| Vomiting | 0 | 4 | 4 |
| Upper abdominal pain | 1 | 3 | 4 |
| Dyspepsia | 2 | 3 | 3 |
| Abdominal discomfort | 0 | 2 | 1 |
| **General disorders and administration site conditions** | | | |
| Fatigue | 4 | 6 | 6 |
| Peripheral edema | 4 | 5 | 8 |
| Asthenia | 2 | 3 | 1 |
| Discomfort | 0 | 0 | 2 |
| **Musculoskeletal and connective tissue disorders** | | | |
| Muscle spasms | 3 | 5 | 3 |
| **Psychiatric disorders** | | | |
| Hallucinations, including visual, auditory and mixed | 1 | 5 | 6 |
| Insomnia | 3 | 4 | 4 |
| Sleep attacks or sudden onset of sleep | 1 | 3 | 6 |
| Sleep disorder | 1 | 2 | 3 |
| Depression | 0 | 2 | 0 |
| Anxiety | 1 | 1 | 4 |
| Restlessness | 0 | 0 | 2 |
| **Injury, poisoning, and procedural complications** | | | |
| Fall | 1 | 4 | 4 |
| **Vascular disorders** | | | |
| Orthostatic hypotension | 1 | 3 | 0 |
| Hypotension | 1 | 0 | 3 |
| **Ear and labyrinth disorders** | | | |
| Vertigo | 1 | 4 | 2 |
| **Metabolism and nutrition disorders** | | | |
| Increased appetite | 1 | 3 | 2 |
| Anorexia | 2 | 2 | 4 |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Cough | 1 | 3 | 3 |
| **Investigations** | | | |
| Weight increased | 0 | 0 | 3 |

Because this study used a flexible dose titration design, it was not possible to assess the effects of dose on the incidence of adverse events.

Adverse events can initially occur in either the titration or maintenance phase. Some adverse events developed in MIRAPEX ER-treated patients during the titration phase and persisted (≥7 days) into the maintenance phase (i.e., MIRAPEX ER % - placebo % = treatment difference ≥2%); persistent adverse events were somnolence, nausea, constipation, fatigue, and dry mouth.

*Impulse control symptoms including compulsive behaviors*

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson's disease, including pramipexole. A total of 539 patients with early Parkinson's disease participated in a MIRAPEX ER placebo-controlled study of 33 weeks duration. In this study patients were specifically asked at each visit about the occurrence of these symptoms. A total of 5 of 223 (2.2%) treated with MIRAPEX ER tablets, 6 of 213 (2.8%) treated with immediate-release pramipexole tablets, and 2 of 103 (2%) treated with placebo reported compulsive behaviors, including pathological gambling, hypersexuality, and/or compulsive buying [*see Patient Counseling Information (17.4)*].

A double-blind, randomized, parallel group trial evaluated the efficacy and tolerability of an overnight switch from immediate-release pramipexole tablets to MIRAPEX ER tablets at the same daily dose in 156 early Parkinson's disease patients with or without levodopa. One of 104 patients switched from immediate-release pramipexole tablets to MIRAPEX ER tablets discontinued due to adverse events (vertigo and nausea).

During the development of MIRAPEX ER tablets, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient in his or her care.

*Other adverse events observed during clinical trials of immediate-release pramipexole tablets*

Adverse events not listed above but reported on at least two occasions (one occasion if the event was serious) in clinical studies involving 2509 individuals who received pramipexole immediate-release tablets are listed below. The reported events are included without regard to determination of a causal relationship to pramipexole immediate-release tablets.

*Blood and lymphatic system disorders:* anemia, iron deficiency anemia, leukocytosis, leukopenia, lymphadenitis, lymphadenopathy, thrombocythaemia, thrombocytopenia

*Cardiac disorders:* angina pectoris, arrhythmia supraventricular, atrial fibrillation, atrioventricular block first degree, atrioventricular block second degree, bradycardia, bundle branch block, cardiac arrest, cardiac failure, cardiac failure congestive, cardiomegaly, coronary artery occlusion, cyanosis, extrasystoles, left ventricular failure, myocardial infarction, nodal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, ventricular fibrillation, ventricular extrasystoles, ventricular hypertrophy

*Congenital, familial, and genetic disorders:* atrial septal defect, congenital foot malformation, spine malformation

*Ear and labyrinth disorders:* deafness, ear pain, hearing impaired, hypoacusis, motion sickness, vestibular ataxia

*Endocrine disorders:* goiter, hyperthyroidism, hypothyroidism

*Eye disorders:* accommodation abnormalities, amaurosis fugax, blepharitis, blepharospasm, cataract, dacryostenosis acquired, diplopia, dry eye, eye hemorrhage, eye irritation, eye pain, eyelid edema, eyelid ptosis, glaucoma, keratitis, macular degeneration, myopia, photophobia, retinal detachment, retinal vascular disorder, scotoma, vision abnormalities, vision blurred, visual acuity reduced, vitreous floaters

*Gastrointestinal disorders:* abdominal discomfort, abdominal distension, aphthous stomatitis, ascites, cheilitis, colitis, colitis ulcerative, diarrhea, dyspepsia, dysphagia, duodenal ulcer, duodenal ulcer hemorrhage, enteritis, eructation, fecal incontinence, gastric ulcer, gastric ulcer hemorrhage, gastritis, gastrointestinal hemorrhage, gastroesophageal reflux disease, gingivitis, haematemesis, haematochezia, hemorrhoids, hiatus hernia, hyperchlorhydria, ileus, inguinal hernia, intestinal obstruction, irritable bowel syndrome, esophageal spasm, esophageal stenosis, esophagitis, pancreatitis, periodontitis, rectal hemorrhage, reflux esophagitis, tongue edema, tongue ulceration, toothache, umbilical hernia

*General disorders:* asthenia, chest discomfort, chills, death, drug withdrawal syndrome, face edema, feeling cold, feeling hot, feeling jittery, fever, gait disturbance, impaired healing, influenza-like illness, irritability, localized edema, edema, malaise, pitting edema, thirst

*Hepatobiliary disorders:* biliary colic, cholecystitis, cholecystitis chronic, cholelithiasis

*Immune system disorders:* drug hypersensitivity

*Infections and infestations:* abscess, acute tonsillitis, appendicitis, bronchiolitis, bronchitis, bronchopneumonia, cellulitis, cystitis, dental caries, diverticulitis, ear infection, eye infection, folliculitis, fungal infection, furuncle, gangrene, gastroenteritis, gingival infection, herpes simplex, herpes zoster, hordeolum, influenza, intervertebral discitis, laryngitis, lobar pneumonia, nail infection, onychomycosis, oral candidiasis, orchitis, osteomyelitis, otitis externa, otitis media, paronychia, pyelonephritis, pyoderma, sepsis, skin infection, tonsillitis, tooth abscess, tooth infection, upper respiratory tract infection, urethritis, vaginal candidiasis, vaginal infection, viral infection, wound infection

*Injury, poisoning, and procedural complications:* accidental falls, drug toxicity epicondylitis, road traffic accident, sunburn, tendon rupture

*Metabolism and nutrition disorders:* cachexia, decreased appetite, decreased weight, dehydration, diabetes mellitus, fluid retention, gout, hypercholesterolemia, hyperglycemia, hyperlipidemia, hyperuricemia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, hypovitaminosis, increased appetite, increased creatine PK, metabolic alkalosis
*Musculoskeletal and connective tissue disorders:* bone pain, bursitis, fasciitis, flank pain, intervertebral disc disorder, intervertebral disc protrusion, joint effusion, joint stiffness, joint swelling, monarthritis, muscle rigidity, muscle spasms, musculoskeletal stiffness, myasthenia, myopathy, myositis, nuchal rigidity, osteoarthritis, osteonecrosis, osteoporosis, pain in extremity, polymyalgia, rheumatoid arthritis, shoulder pain, spinal osteoarthritis, tendonitis, tenosynovitis, twitching
*Neoplasms benign, malignant, and unspecified:* abdominal neoplasm, adenocarcinoma, adenoma benign, basal cell carcinoma, bladder cancer, breast cancer, breast neoplasm, chronic lymphocytic leukemia, colon cancer, colorectal cancer, endometrial cancer, gallbladder cancer, gastric cancer, gastrointestinal neoplasm, hemangioma, hepatic neoplasm, hepatic neoplasm malignant, lip and/or oral cavity cancer, lung neoplasm malignant, lung cancer metastatic, lymphoma, malignant melanoma, melanocytic naevus, metastases to lung, multiple myeloma, oral neoplasm benign, neoplasm, neoplasm malignant, neoplasm prostate, neoplasm skin, neuroma, ovarian cancer, prostate cancer, prostatic adenoma, pseudo lymphoma, renal neoplasm, skin cancer, skin papilloma, squamous cell carcinoma, thyroid neoplasm, uterine leiomyoma
*Nervous system disorders:* ageusia, akinesia, amnesia, akathisia, anticholinergic syndrome, aphasia, balance disorder, brain edema, carotid artery occlusion, carpal tunnel syndrome, cerebral artery embolism, cerebral hemorrhage, cerebral infarction, cerebral ischemia, chorea, cognitive disorder, coma, convulsion, coordination abnormal, dementia, depressed level of consciousness, disturbance in attention, dizziness postural, dysarthria, dysgraphia, dystonia, extrapyramidal syndrome, facial palsy, grand mal convulsion, hemiplegia, hyperaesthesia, hyperkinesia, hyperreflexia, hyporeflexia, hypertonia, hypesthesia, hypotonia, lethargy, loss of consciousness, memory impairment, migraine, muscle contractions involuntary, myoclonus, narcolepsy, neuralgia, neuropathy, nystagmus, parosmia, psychomotor hyperactivity, sciatica, sedation, sensory disturbance, sleep phase rhythm disturbance, sleep talking, stupor, syncope vasovagal, tension headache, thinking abnormalities
*Psychiatric disorders:* affect lability, aggression, agitation, bradyphrenia, bruxism, suicide, delirium, delusions, delusional disorder persecutory type, disorientation, dissociation, emotional distress, euphoric mood, hallucination auditory, hallucination visual, initial insomnia, insomnia, libido increased, mania, middle insomnia, mood altered, nightmare, obsessive thoughts, obsessive-compulsive disorder, panic reaction, paranoid reaction, parasomnia, personality disorder, psychotic disorder, restlessness, sleep disorders, sleep walking, suicidal ideation
*Renal and urinary disorders:* chromaturia, dysuria, glycosuria, hematuria, urgency, nephrolithiasis, neurogenic bladder, nocturia, oliguria, pollakiuria, proteinuria, renal artery stenosis, renal colic, renal cyst, renal failure, renal impairment, urinary frequency, urinary incontinence, urinary retention, urinary tract infection
*Reproductive system and breast disorders:* amenorrhea, breast pain, dysmenorrhea, epididymitis, gynaecomastia, impotence, menopausal symptoms, menorrhagia, metrorrhagia, ovarian cyst, priapism, prostatitis, sexual dysfunction, uterine hemorrhage, vaginal discharge, vaginal hemorrhage
*Respiratory, thoracic, and mediastinal disorders:* apnea, aspiration, asthma, choking, chronic obstructive pulmonary disease, dry throat, dysphonia, dyspnea exertional, epistaxis, haemoptysis, hiccups, hyperventilation, increased bronchial secretion, laryngospasm, nasal congestion, nasal dryness, nasal polyps, obstructive airways disorder, pharyngolaryngeal pain, pleurisy, pneumonia, pneumonia aspiration, pneumothorax, postnasal drip, productive cough, pulmonary embolism, pulmonary edema, respiratory alkalosis, respiratory distress, respiratory failure, respiratory tract congestion, rhinitis allergic, rhinorrhea, sinus congestion, sleep apnoea syndrome, sneezing, snoring, tachypnea, wheezing
*Skin and subcutaneous tissue disorders:* acne, alopecia, cold sweat, dermal cyst, dermatitis, dermatitis bullous, dermatitis contact, dry skin, ecchymosis, eczema, erythema, hyperkeratosis, livedo reticularis, night sweats, periorbital edema, petechiae, photosensitivity allergic reaction, psoriasis, purpura, rash erythematous, rash maculo-papular, rash papular, rosacea, seborrhea, seborrheic dermatitis, skin burning sensation, skin discoloration, skin disorders, skin exfoliation, skin hyperpigmentation, skin hypertrophy, skin irritation, skin nodule, skin odor abnormal, skin ulcer, urticaria
*Vascular disorders:* aneurysm, angiopathy, arteriosclerosis, circulatory collapse, deep vein thrombosis, embolism, hematoma, hot flush, hypertensive crisis, lymphoedema, pallor, phlebitis, Raynaud's phenomenon, shock, thrombophlebitis, thrombosis, varicose vein

### 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of immediate-release pramipexole tablets, primarily in Parkinson's disease patients. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to pramipexole tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA terminology: abnormal behavior, abnormal dreams, accidents (including fall), blackouts, compulsive shopping, fatigue, hallucinations (all kinds), headache, hypotension (including postural hypotension), increased eating (including binge eating, compulsive eating, and hyperphagia), libido disorders (including increased and decreased libido, and hypersexuality), pathological gambling, pruritus, syncope, vomiting, and weight increase.

## 7 DRUG INTERACTIONS

No drug interaction studies were conducted with MIRAPEX ER tablets since the potential for drug interactions mainly depends on the active drug substance pramipexole and not the formulation. Data are available for the immediate-release pramipexole tablet formulation [*see Clinical Pharmacology (12.3)*].

### 7.1 Dopamine Antagonists

Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX ER tablets.

### 7.2 Drug/Laboratory Test Interactions

There are no known interactions between pramipexole and laboratory tests.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

*Pregnancy Category C*

There are no adequate and well-controlled studies in pregnant women. MIRAPEX ER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day [5 times the maximum recommended human dose (MRHD) on a $mg/m^2$ basis]. Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be due to the prolactin-lowering effect of pramipexole, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 70 times that in humans at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the MRHD on a $mg/m^2$ basis) or greater during the latter part of pregnancy and throughout lactation.

### 8.3 Nursing Mothers

A single-dose, radio-labeled study showed that drug-related material was present in rat milk at concentrations three to six times higher than in plasma at equivalent time points.

Studies have shown that pramipexole treatment resulted in an inhibition of prolactin secretion in humans and rats.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The pharmacokinetics, safety, and efficacy of MIRAPEX ER tablets in pediatric patients have not been evaluated.

### 8.5 Geriatric Use

Pramipexole total oral clearance is approximately 30% lower in subjects older than 65 years compared with younger subjects, because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In a placebo-controlled clinical trial of MIRAPEX ER tablets in early Parkinson's disease, 47% of the 259 patients were ≥65 years of age. Among patients receiving MIRAPEX ER tablets, hallucinations were more common in the elderly, occurring in 13% of the patients ≥65 years of age compared to 2% of the patients <65 years of age.

### 8.6 Patients with Renal Impairment

The elimination of pramipexole is dependent upon renal function. Pramipexole clearance is extremely low in dialysis patients, as a negligible amount of pramipexole is removed by dialysis [*see Dosage and Administration (2.2), Warnings and Precautions (5.5), and Clinical Pharmacology (12.3)*].

## 9 DRUG ABUSE AND DEPENDENCE

### 9.1 Controlled Substance

Pramipexole is not a controlled substance.

### 9.2 Abuse and Dependence

Pramipexole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, in a rat model of cocaine self-administration, pramipexole had little or no effect.

## 10 OVERDOSAGE

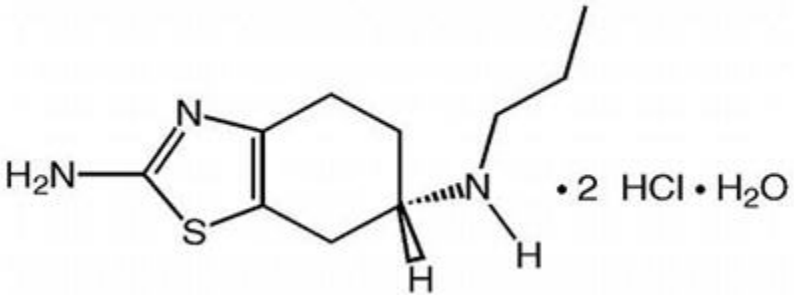
There is no clinical experience with significant overdosage. One patient took 11 mg/day of pramipexole for 2 days in a clinical trial for an investigational use. Blood pressure remained stable, although pulse rate increased to between 100 and 120 beats/minute. No other adverse events were reported related to the increased dose.

There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring.

## 11 DESCRIPTION

MIRAPEX ER tablets contain pramipexole, a non-ergot dopamine agonist. The chemical name of pramipexole dihydrochloride is (*S*)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzothiazole dihydrochloride monohydrate. Its empirical formula is $C_{10}H_{17}N_3S \cdot 2HCl \cdot H_2O$, and its molecular weight is 302.26.

The structural formula is:




Pramipexole dihydrochloride is a white to off-white powder substance. Melting occurs in the range of 296°C to 301°C, with decomposition. Pramipexole dihydrochloride is more than 20% soluble in water, about 8% in methanol, about 0.5% in ethanol, and practically insoluble in dichloromethane.

MIRAPEX ER tablets, for oral administration, contain 0.375 mg, 0.75 mg, 1.5 mg, 3 mg, or 4.5 mg of pramipexole dihydrochloride monohydrate. Inactive ingredients are hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Pramipexole is a non-ergot dopamine agonist with high relative *in vitro* specificity and full intrinsic activity at the $D_2$ subfamily of dopamine receptors, binding with higher affinity to $D_3$ than to $D_2$ or $D_4$ receptor subtypes.

The precise mechanism of action of pramipexole as a treatment for Parkinson's disease is unknown, although it is believed to be related to its ability to stimulate dopamine receptors in the striatum. This conclusion is supported by electrophysiologic studies in animals that have demonstrated that pramipexole influences striatal neuronal firing rates via activation of dopamine receptors in the striatum and the substantia nigra, the site of neurons that send projections to the striatum. The relevance of $D_3$ receptor binding in Parkinson’s disease is unknown.

### 12.2 Pharmacodynamics

The effect of pramipexole on the QT interval of the ECG was investigated in a clinical study in 60 healthy male and female volunteers. All subjects initiated treatment with 0.375 mg MIRAPEX ER tablets administered once daily, and were up-titrated every 3 days to 2.25 mg and 4.5 mg daily. No dose- or exposure-related effect on mean QT intervals was observed: however the study did not have a valid assessment of assay sensitivity. The effect of pramipexole on QTc intervals at higher exposures achieved either due to drug interactions (e.g., with cimetidine), renal impairment, or at higher doses has not been systematically evaluated. Although mean values remained within normal reference ranges throughout the study, supine systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate for subjects treated with pramipexole generally increased during the up-titration phase, up to 10 mmHg, 7 mmHg, and 10 bpm higher than placebo, respectively. Higher SBP, DBP, and pulse rates compared to placebo were maintained until the pramipexole doses were tapered; values on the last day of tapering were generally similar to baseline values. Such effects have not been observed in clinical studies with Parkinson’s disease patients, and are most likely due to the forced up-titration every 3 days.

### 12.3 Pharmacokinetics

MIRAPEX ER tablets, like immediate-release pramipexole tablets, display linear pharmacokinetics over the entire clinical dosage range. Slow release of pramipexole from MIRAPEX ER tablets with once-daily administration results in the same daily maximum and minimum pramipexole plasma concentrations ($C_{max}$, $C_{min}$) as three times daily administration of immediate-release pramipexole tablets.

*Absorption*

The absolute bioavailability of pramipexole is greater than 90%, indicating that it is well absorbed and undergoes little presystemic metabolism.
Increase in systemic exposure of pramipexole following oral administration of 0.375 mg to 4.5 mg of MIRAPEX ER tablets was dose-proportional. For MIRAPEX ER tablets, steady state of exposure is reached within 5 days of continuous dosing.
Relative bioavailability of MIRAPEX ER tablets compared with immediate-release tablets was approximately 100%. In a repeat-dose study in healthy, normal volunteers, MIRAPEX ER tablets 4.5 mg administered once daily was bioequivalent with regard to $C_{max}$ and AUC over 24 hours to immediate-release pramipexole tablets 1.5 mg administered three times daily. The average time-to-peak concentration for MIRAPEX ER tablets is 6 hours. Administration of MIRAPEX ER tablets with food (i.e., high-fat meal) did not affect AUC but increased $C_{max}$ by approximately 20% and delayed $T_{max}$ by approximately 2 hours compared with dosing under fasted conditions; these differences are not considered to be clinically relevant [*see Dosage and Administration (2.1)*].
*Distribution*
Pramipexole is extensively distributed, having a volume of distribution of about 500 L (coefficient of variation [CV] = 20%). It is about 15% bound to plasma proteins. Pramipexole distributes into red blood cells as indicated by an erythrocyte-to-plasma ratio of approximately 2.
*Metabolism*
Pramipexole is metabolized only to a negligible extent (<10%). No specific active metabolite has been identified in human plasma or urine.
*Elimination*
Urinary excretion is the major route of pramipexole elimination, with 90% of a pramipexole dose recovered in urine, almost all as unchanged drug. The renal clearance of pramipexole is approximately 400 mL/min (CV=25%), approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.
*Pharmacokinetics in Specific Populations*
Because therapy with MIRAPEX ER tablets is initiated at a low dose and gradually titrated upward according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the initial dose based on gender, weight, race, or age is not necessary. However, renal insufficiency causes a large decrease in the ability to eliminate pramipexole. This will necessitate dosage adjustment in patients with moderate to severe renal impairment [*see Dosage and Administration (2.2)*].
Gender
Pramipexole clearance is about 30% lower in women than in men, but this difference can be accounted for by differences in body weight. There is no difference in plasma half-life between males and females.
Age
Pramipexole clearance is reduced by approximately 30% in the elderly (aged 65 years or older) compared with young, healthy volunteers (aged less than 40 years). This difference is most likely due to the reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance.
Race
No racial differences in metabolism and elimination have been identified.
Hepatic Impairment
The influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated. Because approximately 90% of the recovered dose is excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.
Renal Impairment
Clearance of immediate-release pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers [*see Dosage and Administration (2.2) and Warnings and Precautions (5.5)*]. In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance.
*Drug Interactions*
No specific pharmacokinetic drug interaction trials were conducted with MIRAPEX ER tablets since the potential for drug interactions mainly depends on the active drug substance pramipexole and not the formulation. The following interaction data were obtained using immediate-release pramipexole tablets.
*Carbidopa/levodopa:* Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa $C_{max}$ by about 40% and a decrease in $T_{max}$ from 2.5 to 0.5 hours.
*Selegiline:* In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole.
*Amantadine:* Population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole.
*Cimetidine:* Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life (N=12).
*Probenecid:* Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12).

*Other drugs eliminated via renal secretion:* Population pharmacokinetic analysis suggests that co-administration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole.

*CYP interactions:* Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes *in vivo* or *in vitro*. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day.

*Drugs affecting gastrointestinal motility or gastric pH:*

Population pharmacokinetic analysis suggests that co-administration of antacids (N=6) decreased the oral clearance of pramipexole by about 25%, while H2-blockers (N=5), anticholinergics (N=27), propulsive (N=7), and proton pump inhibitors (N=16) are likely to have little effect on the oral clearance of pramipexole.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to mice at doses up to 10 mg/kg/day [or approximately 10 times the maximum recommended human dose (MRHD) of 1.5 mg TID on a $mg/m^2$ basis]. Pramipexole was administered in the diet to rats at doses up to 8 mg/kg/day. These doses were associated with plasma AUCs up to approximately 12 times that in humans at the MRHD. No significant increases in tumors occurred in either species. Pramipexole was not mutagenic or clastogenic in a battery of *in vitro* (bacterial reverse mutation, V79/HGPRT gene mutation, chromosomal aberration in CHO cells) and *in vivo* (mouse micronucleus) assays.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a $mg/m^2$ basis) prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

### 13.2 Animal Toxicology and/or Pharmacology

*Retinal Pathology in Albino Rats*

Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study with pramipexole. These findings were first observed during week 76 and were dose-dependent in animals receiving 2 or 8 mg/kg/day (plasma AUCs equal to 2.5 and 12.5 times that in humans at the MRHD of 1.5 mg TID). In a similar study of pigmented rats with 2-years exposure to pramipexole at 2 or 8 mg/kg/day, retinal degeneration was not observed. Animals given drug had thinning in the outer nuclear layer of the retina that was only slightly greater than that seen in control rats.

Investigative studies demonstrated that pramipexole reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats, which was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on a $mg/m^2$ basis) and constant light (100 lux), but not in pigmented rats exposed to the same dose and higher light intensities (500 lux). Thus, the retina of albino rats is considered to be uniquely sensitive to the damaging effects of pramipexole and light. Similar changes in the retina did not occur in a 2-year carcinogenicity study in albino mice treated with 0.3, 2, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a $mg/m^2$ basis). Evaluation of the retinas of monkeys given 0.1, 0.5, or 2.0 mg/kg/day of pramipexole (0.4, 2.2, and 8.6 times the highest clinical dose on a $mg/m^2$ basis) for 12 months and minipigs given 0.3, 1, or 5 mg/kg/day of pramipexole for 13 weeks also detected no changes.

The potential significance of this effect in humans has not been established, but cannot be disregarded because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved.

*Fibro-osseous Proliferative Lesions in Mice*

An increased incidence of fibro-osseous proliferative lesions occurred in the femurs of female mice treated for 2 years with 0.3, 2.0, or 10 mg/kg/day (0.3, 2.2, and 11 times the highest clinical dose on a $mg/m^2$ basis). Lesions occurred at a lower rate in control animals. Similar lesions were not observed in male mice or rats and monkeys of either sex that were treated chronically with pramipexole. The significance of this lesion to humans is not known.

## 14 CLINICAL STUDIES

The effectiveness of MIRAPEX ER tablets in the treatment of early Parkinson's disease was supported by clinical pharmacokinetic data [*see Clinical Pharmacology (12.3)*], and by a single randomized, double-blind, placebo-controlled multicenter clinical trial. A second study evaluated an overnight switch from immediate-release pramipexole tablets to MIRAPEX ER tablets.

In both randomized studies, the Unified Parkinson's Disease Rating Scale (UPDRS) served as a primary outcome assessment measure. The UPDRS is a four-part multi-item rating scale intended to evaluate mentation (Part I), activities of daily living (Part II), motor performance (Part III), and complications of therapy (Part IV).

Part II of the UPDRS contains 13 questions related to activities of daily living, which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 14 items designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability, etc.), scored for different body regions and has a maximum (worst) score of 108.

The effectiveness of MIRAPEX ER tablets in early Parkinson's disease patients (Hoehn & Yahr Stages I-III) who were not on levodopa therapy was established in a randomized, double-blind, placebo-controlled, 3-parallel-group clinical study. Patients were treated with MIRAPEX ER tablets, immediate-release pramipexole tablets, or placebo; those treated with MIRAPEX ER tablets or immediate-release pramipexole tablets had a starting dose of 0.375 mg/day followed by a flexible up-titration, based on efficacy and tolerability, up to 4.5 mg/day. Levodopa was permitted during the study as rescue medication. Stable doses of concomitant MAO-B inhibitors, anticholinergics, or amantadine, individually or in combination, were allowed. The primary efficacy endpoint was the mean change from baseline in the UPDRS Parts II+III score for MIRAPEX ER tablets versus placebo following 18 weeks of treatment.

At 18 weeks of treatment, the mean change from baseline UPDRS Parts II+III score was –8.1 points in patients receiving MIRAPEX ER tablets (n=102) and –5.1 points in patients receiving placebo (n=50), a difference that was statistically significant ($p<0.03$). Seven patients treated with placebo (14%) and 3 patients treated with MIRAPEX ER tablets (3%) received levodopa rescue medication. At 18 weeks, the mean dose of MIRAPEX ER was 3 mg/day.

No differences in effectiveness based on age or gender were detected. Patients receiving MAOB-I, anticholinergics, or amantadine had responses similar to patients not receiving these drugs.

A randomized, double-blind, parallel group trial was conducted in 156 Parkinson's disease patients (Hoehn & Yahr Stages I-III) to assess overnight switching of immediate-release pramipexole tablets to MIRAPEX ER tablets; stable doses of concomitant levodopa, MAOB-I, anticholinergics, or amantadine, individually or in combination, were allowed. Patients in this study had a mean disease duration of approximately 3.5 years. Patients at stable doses of immediate-release pramipexole tablets were randomized to receive the same daily dose of blinded MIRAPEX ER tablets (n=104) or blinded immediate-release pramipexole tablets (n=52). Following 4 weeks of treatment, the study medication dose could be adjusted depending on efficacy and tolerability.

Of the 104 patients randomized to cross over to MIRAPEX ER, 85% (n=87) were switched with no worsening of the UPDRS II+III by more than 15% compared to 94% (n=49) of 52 patients maintained on immediate-release pramipexole. Some patients required dose adjustment. This study, as designed, cannot adequately assess whether or not patients switched to Mirapex ER achieved equivalent control of their parkinsonian symptoms as compared to those continuing on immediate-release pramipexole.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

MIRAPEX ER tablets are available as follows:

**0. 375 mg:** white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.375" on the other side.

Unit of Use Bottles of 30 NDC 0597-0109-30

**0.75 mg:** white to off-white, round, bevel-edged, extended-release tablets debossed with "ER" on one side and "0.75" on the other side.

Unit of Use Bottles of 30 NDC 0597-0285-30

**1.5 mg:** white to off-white, oval, extended-release tablets debossed with "ER" on one side and "1.5" on the other side.

Unit of Use Bottles of 30 NDC 0597-0113-30

**3 mg:** white to off-white, oval, extended-release tablets debossed with "ER" on one side and "3.0" on the other side.

Unit of Use Bottles of 30 NDC 0597-0115-30

**4.5 mg:** white to off-white, oval, extended-release tablets debossed with "ER" on one side and "4.5" on the other side.

Unit of Use Bottles of 30 NDC 0597-0116-30

*Storage*

**Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F)** [see USP Controlled Room Temperature]. Protect from exposure to high humidity. Store in a safe place out of the reach of children.

## 17 PATIENT COUNSELING INFORMATION

*See FDA-Approved Patient Labeling*

### 17.1 Dosing Instructions

Instruct patients to take MIRAPEX ER tablets only as prescribed. If a dose is missed, advise patients not to double their next dose. MIRAPEX ER tablets can be taken with or without food. If patients develop nausea, advise that taking MIRAPEX ER tablets with food may reduce the occurrence of nausea.

MIRAPEX ER tablets should be swallowed whole. They should not be chewed, crushed, or divided [*see Dosage and Administration (2.1)*].

Pramipexole is the active ingredient that is in both MIRAPEX ER tablets and immediate-release pramipexole tablets. Ensure that patients do not take both immediate-release pramipexole and MIRAPEX ER.

### 17.2 Sedating Effects

Alert patients to the potential sedating effects of MIRAPEX ER tablets, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with MIRAPEX ER tablets to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., conversations or eating) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician. Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX ER and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine) [*see Warnings and Precautions (5.1)*].

### 17.3 Hallucinations

Inform patients that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease [*see Warnings and Precautions (5.3)*].

### 17.4 Impulse Control Symptoms Including Compulsive Behaviors

There have been reports of patients experiencing intense urges to gamble, increased sexual urges, other intense urges, and the inability to control these urges while taking one or more of the medications that increase central dopaminergic tone, that are generally used for the treatment of Parkinson’s disease, including pramipexole. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges, or other urges while being treated with MIRAPEX ER tablets. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges, or other intense urges while taking MIRAPEX ER tablets. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking MIRAPEX ER tablets [*see Adverse Reactions (6.1)*].

### 17.5 Postural (Orthostatic) Hypotension

Advise patients that they may develop postural (orthostatic) hypotension, with or without symptoms such as dizziness, nausea, fainting, or blackouts, and sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, caution patients against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with MIRAPEX ER [*see Warnings and Precautions (5.2)*].

### 17.6 Pregnancy

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, advise women to notify their physicians if they become pregnant or intend to become pregnant during therapy [*see Use in Specific Populations (8.1)*].

### 17.7 Nursing Mothers

Because of the possibility that pramipexole may be excreted in breast milk, advise women to notify their physicians if they intend to breast-feed or are breast-feeding an infant [*see Use in Specific Populations (8.3)*].

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**Patient Information**

Mirapex® ER™ ***[mîr#-ah-p#x]*** (pramipexole dihydrochloride) extended-release tablets

**Read the Patient Information that comes with MIRAPEX ER tablets before you start taking it and each time you refill your prescription. The information may have changed. This leaflet does not take the place of discussions with your doctor about your medical condition or your treatment.**

**What is MIRAPEX ER?**

MIRAPEX ER tablets are a prescription medicine to treat the signs and symptoms of early Parkinson's disease.
MIRAPEX ER tablets have not been studied in children. It is not known if MIRAPEX ER tablets are safe or effective in children. Please speak to your doctor for more information about why MIRAPEX ER tablets were prescribed for you.

**Who should not take MIRAPEX ER?**

You should not take MIRAPEX ER tablets if you are allergic (hypersensitive) to the active ingredient (pramipexole) or any of the other ingredients listed at the end of this leaflet.

**What should I tell my doctor before taking MIRAPEX ER?**

- **Before taking MIRAPEX ER, tell your doctor about all of your medical conditions, including if you**
- feel sleepy during the day, if you use any medications that make you sleepy, or are taking any medication which your doctor informs you may increase the effects of MIRAPEX ER, such as cimetidine.
- have low blood pressure, or if you feel dizzy or faint, especially when getting up from a lying or sitting position.
- have trouble controlling your muscles (dyskinesia).
- have kidney problems.
- are pregnant or plan to become pregnant. Based on animal data, MIRAPEX ER may harm your unborn baby.
- are breastfeeding. It is not known if MIRAPEX ER tablets will pass into your breast milk. You and your doctor should decide if you will take MIRAPEX ER tablets or breast-feed. You should not do both.
- drink alcohol. Alcohol can increase the chance that MIRAPEX ER tablets will make you feel sleepy or fall asleep when you should be awake.

- **Tell your doctor about all the medicines you take, including:**
- any prescription and non-prescription medicines. **Especially tell your doctor if you take any other medicines that make you sleepy.**
- any non-prescription medicines, including vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new prescription. MIRAPEX ER tablets and other medicines may interact with each other causing side effects. MIRAPEX ER tablets may affect the way other medicines work, and other medicines may affect how MIRAPEX ER tablets work.

**How should I take MIRAPEX ER?**

- Follow your doctor’s directions carefully. MIRAPEX ER is taken once daily. Your doctor will tell you how to use MIRAPEX ER tablets.

- Your doctor may change your dose until you are taking the right amount of medicine to help control your symptoms. Do not take more or less MIRAPEX ER tablets than your doctor tells you to.

- Swallow tablets whole. Do not chew, crush, or divide MIRAPEX ER tablets.

- MIRAPEX ER tablets can be taken with or without food. Taking MIRAPEX ER tablets with food may lower your chances of getting nausea.

- If you miss a dose, **do not double your next dose**. Skip the dose you missed and take your next regular dose.

- If you have Parkinson’s disease and are stopping MIRAPEX ER tablets, you should stop MIRAPEX ER tablets slowly over 7 days. Do not suddenly stop taking MIRAPEX ER tablets without talking to your healthcare provider. If you stop this medicine suddenly, you may develop fever, confusion, or severe muscle stiffness. Be sure to tell your doctor right away if you stop taking MIRAPEX ER tablets for any reason. Do not start taking MIRAPEX ER tablets again before speaking with your doctor.

**What important safety information should I know about MIRAPEX ER?**

Please read this document carefully; many sections contain safety information.
This medicine was prescribed for you by your doctor for your condition. Do not use it for another condition or give the medicine to others.
Pramipexole is the active ingredient that is in both MIRAPEX ER tablets and immediate-release pramipexole tablets. Be sure that you do not take **both** immediate-release pramipexole (MIRAPEX) **and** MIRAPEX ER.

- **Falling asleep during normal activities**. MIRAPEX ER tablets may cause you to fall asleep while you are doing daily activities such as driving, talking with other people, or eating.

  Some people taking the medicine in MIRAPEX ER tablets have had car accidents because they fell asleep while driving.

  Some patients did not feel sleepy before they fell asleep while driving. You could fall asleep without any warning.

  **Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how MIRAPEX ER tablets affect you. Sleepiness caused by MIRAPEX ER may first occur as late as one year after initiation of treatment.**

**Tell your doctor right away if you fall asleep while you are doing activities such as talking with people, eating, or driving, or if you feel sleepier than is normal for you.**

- **Hallucinations**. Hallucinations (unreal visions, sounds, or sensations) can occur in patients taking MIRAPEX ER tablets. The chances of having hallucinations are higher in patients with Parkinson's disease who are elderly (defined in this case as age 65 or older). If you have hallucinations, talk with your healthcare provider.

- **Unusual urges**. Some patients taking certain medicines to treat Parkinson's disease, including MIRAPEX ER tablets, have reported problems, such as gambling, compulsive eating, compulsive buying, and increased sex drive. If you or your family members notice that you are developing unusual urges or behaviors, talk to your doctor.

- **Melanoma**. Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma, a form of skin cancer, when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the medicines used to treat Parkinson's disease. MIRAPEX ER tablets are one of the medicines used to treat Parkinson's disease; therefore, patients being treated with MIRAPEX ER tablets should have periodic skin examinations.

**What are the possible side effects of MIRAPEX ER?**
**MIRAPEX ER tablets can cause serious side effects, including:**
- **falling asleep during normal daily activities**. See "**What important safety information should I know about MIRAPEX ER?**"

- **low blood pressure when you sit or stand up quickly**. You may have dizziness, nausea, fainting, or sweating. Sit and stand up slowly after you have been sitting or lying down for a while.

- **hallucinations**. You may see, hear, feel, or taste something that isn't there. You have a higher chance of having hallucinations if you are over 65 years old.

- **unusual urges.** See "**What important safety information should I know about MIRAPEX ER?**"

The most common side effects in people taking MIRAPEX ER tablets for Parkinson's disease are sleepiness, nausea and vomiting, constipation, dizziness, fatigue, hallucinations, dry mouth, muscle spasms, and edema (swelling of the feet and ankles).
These are not all the possible side effects of MIRAPEX ER tablets. Tell your doctor if you have any side effect that bothers you. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088, or by visiting www.fda.gov/medwatch.
**What should I avoid while taking MIRAPEX ER?**
- **Do not drive a car, operate a machine, or do anything that needs you to be alert until you know how MIRAPEX ER affects you. Sleepiness caused by MIRAPEX ER may first occur as late as one year after initiation of treatment. See "What important safety information should I know about MIRAPEX ER?"**

- Do not drink alcohol while taking MIRAPEX ER tablets. It can increase your chances of feeling sleepy or falling asleep when you should be awake.

**How should I store MIRAPEX ER?**
- Store MIRAPEX ER tablets at room temperature [77°F (25°C)]. Short-term exposure to higher or lower temperatures [from 59°F (15°C) to 86°F (30°C)] is acceptable. Ask your doctor or pharmacist if you have any questions about storing your tablets.

- Protect from exposure to high humidity.

- **Keep MIRAPEX ER tablets and all medicines out of the reach of children.**

**What does MIRAPEX ER look like?**
These pictures show what MIRAPEX ER tablets look like. Notice that each strength tablet looks different. Immediately call your pharmacist if you receive a MIRAPEX ER tablet that does not look like one of the tablets shown below, as you may have received the wrong medication.

| Strength | Front | Back |
|---|---|---|
| 0.375 mg |   |   |

| | | |
|---|---|---|
| 0.75 mg |   |   |
| 1.5 mg |   |   |
| 3 mg |   |   |
| 4.5 mg |   |   |

Tablets not actual size.

**Other Information about MIRAPEX ER**

This Patient Information leaflet summarizes the most important information about MIRAPEX ER tablets. If you would like more information, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for more information about MIRAPEX ER tablets that is written for healthcare professionals. For more information, call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

**What are the ingredients in MIRAPEX ER?**

**Active Ingredient**: pramipexole dihydrochloride monohydrate.

**Inactive Ingredients**: hypromellose, corn starch, carbomer homopolymer, colloidal silicon dioxide, and magnesium stearate.

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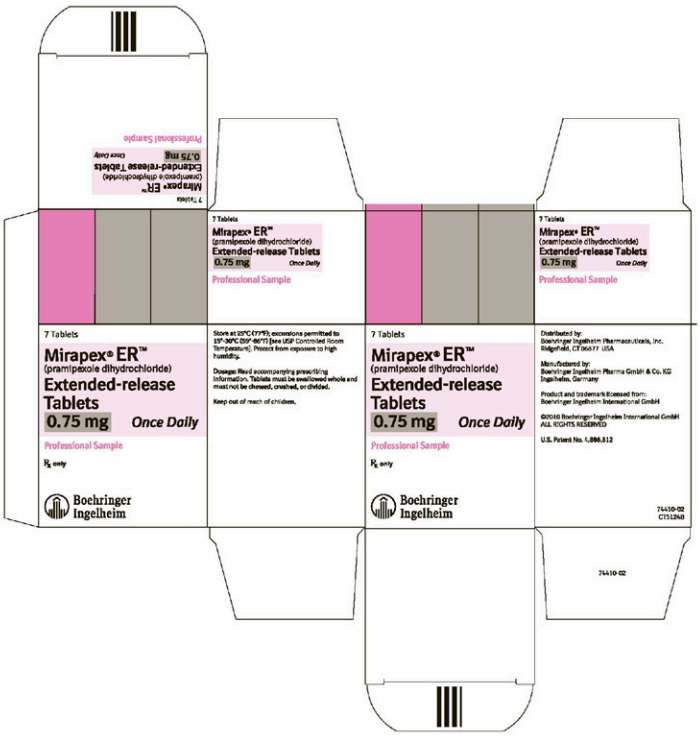
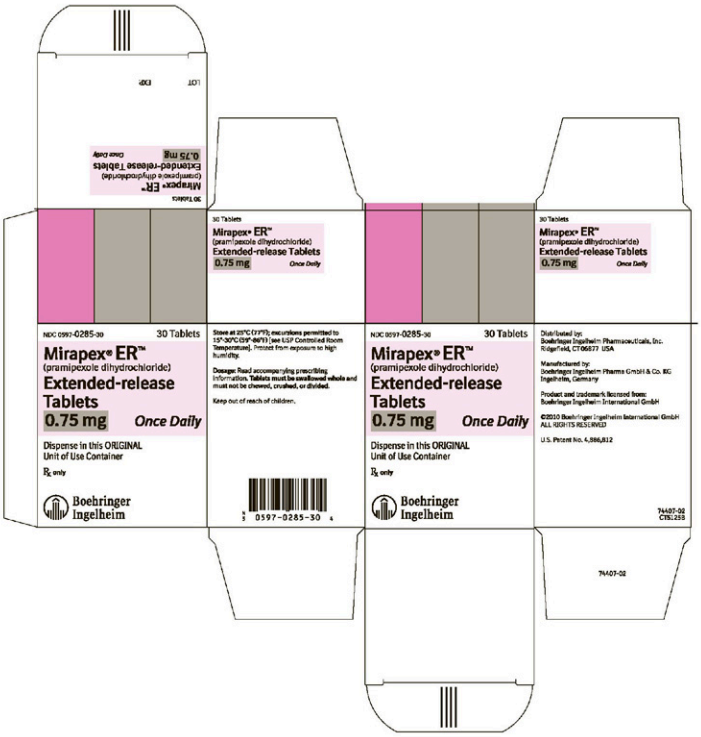
Boehringer Ingelheim International GmbH
U.S. Patent No. 4,886,812

Rev: February 2010
OT220011DB1710
74988-01

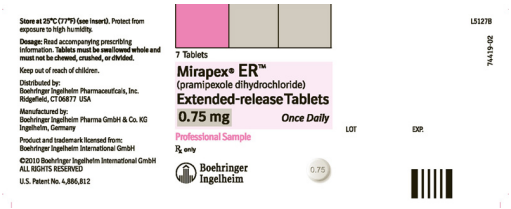
Mirapex ER
0.75 mg Tablets
NDC 0597-0285-07



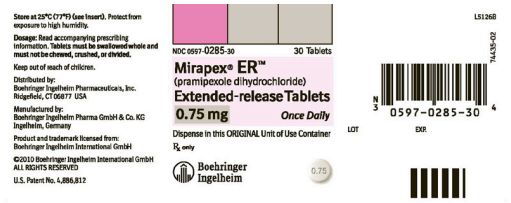

Mirapex ER
0.75 mg Tablets
NDC 0597-0285-30




Mirapex ER
0.75 mg Tablets
NDC 0597-0285-07




Mirapex ER
0.75 mg Tablets
NDC 0597-0285-30

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